


# Endoscopic Endonasal Transsphenoidal Approach for the Surgical Treatment of Pituitary Apoplexy and Clinical Outcomes

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## Abstract

**Purpose:** This study investigated the clinical manifestations, surgical method, and treatment outcomes of patients with pituitary apoplexy and evaluated the safety and effectiveness of the endoscopic endonasal transsphenoidal approach in the treatment of pituitary adenomas. **Patients and methods:** In this retrospective study, we analyzed the data of patients with symptomatic pituitary apoplexy who received surgical treatment by endoscopic endonasal transsphenoidal approach from January 2017 to June 2020 at the Department of Neurosurgery of the First Affiliated Hospital of Bengbu Medical College. Patients were followed up through outpatient visits and telephone interviews. **Results:** Data for 24 patients including 13 males and 11 females with an average age of 46.46 years were analyzed. Headache (83.33%) and visual disturbances (75.00%) were the most common preoperative manifestations. In the 24 patients, 21 (87.50%) tumors were completely removed and 3 (12.50%) were partly removed. Intractable headache improved in all patients over a mean follow-up time of 25.16 months, and postoperative improvement in visual acuity was achieved in 17 of 18 patients (94.44%) with vision defects. Four patients (16.67%) experienced transient urinary collapse after the operation. No intracranial infection, carotid artery injury, or death occurred. **Conclusion:** The endoscopic endonasal transsphenoidal approach is a safe and effective method for the treatment of pituitary apoplexy.

## Keywords

pituitary apoplexy, endoscopic, safe, loss of vision, headache

## Abbreviations

ACTH, adrenocorticotropic hormone; CSF, cerebrospinal fluid; CT, computed tomography; EETA, endonasal transsphenoidal approach; GH, growth hormone; MRI, magnetic resonance imaging; PA, pituitary apoplexy; PRL, prolactin; GTR, gross total removal; NTR, near-total resection; STR, sub-total resection.

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## Introduction

Pituitary apoplexy (PA) is a rare and life-threatening complication in neurosurgery with an incidence rate of 6.2/100 000<sup>1</sup> that occurs in 0.6% to 10% of all pituitary adenomas, with a higher frequency in men.<sup>2,3</sup> PA is most common in nonfunctioning macroadenomas, followed by prolactinomas<sup>4</sup>; a small number of pituitary microadenoma apoplexies have also been reported.<sup>5</sup> The physiologic mechanism of PA is not fully understood, but multiple factors including hypertension, cardiac surgery, coagulation disorders, pituitary stimulation test, pregnancy, and head trauma are thought to contribute.<sup>6-11</sup>

PA manifests as sudden hemorrhage or infarction of pituitary adenomas accompanied by a thunderclap-like headache, decreased vision, ophthalmoplegia, and even disorder of consciousness.<sup>12</sup> Once diagnosed, PA is managed with fluid, electrolytes, and steroid hormones. Patients with significantly

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reduced vision, symptoms of cranial hypertension, and confusion require early surgical intervention. With the development of neuroendoscopy, an endoscopic sphenoidal approach has been used for treatment at an increasing number of medical centers.<sup>13,14</sup> Here we report the clinical manifestations, surgical methods, and treatment outcomes of 24 cases of PA treated by endoscopic endonasal transsphenoidal approach (EETA).

## Material and Methods

Our study was approved by the Research Ethics Committee of Bengbu Medical College (No. 2020025). The need for informed consent was waived by the Research Ethics Committee because the study was retrospective. The confidentiality of patient data was protected in accordance with the tenets of the Declaration of Helsinki.

### Patients and Clinical Assessments

Cases of PA treated with EETA at the Department of Neurosurgery of the First Affiliated Hospital of Bengbu Medical College from January 2017 to June 2020 were retrospectively analyzed. All patients presented with typical clinical symptoms including headache, decreased vision, and ophthalmoplegia. All patients underwent neurologic, endocrine, and ophthalmic evaluations upon admission (Table 1). Based on these results, a retrospective PA Grading System was determined for each patient.<sup>15</sup> Coronal, sagittal, and axial 2-mm thin-slice computerized tomography (CT) scans were carried out for each patient to examine the paranasal sinus and sellar floor bone. Magnetic resonance imaging (MRI) with gadolinium enhancement was performed to evaluate tumor size and infiltration of the cavernous sinus according to the Knosp classification.<sup>16</sup>

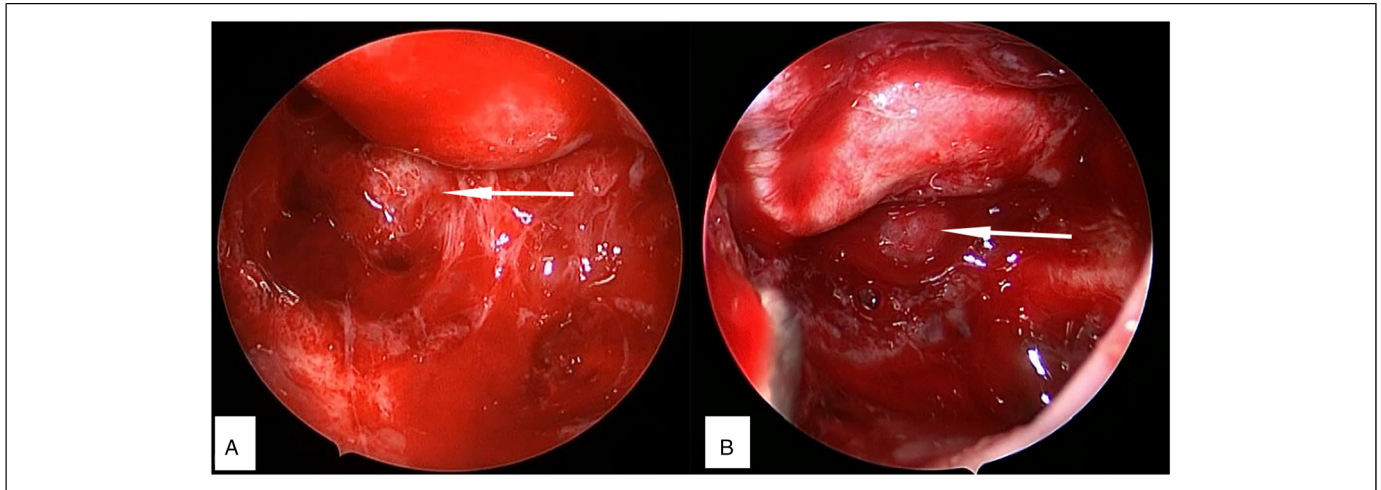
**Table 1.** Demographic and Clinical Characteristics of 24 Patients with Pituitary Apoplexy.

Characteristic	Number (%)
Sex	
Male	13 (54.17%)
Female	11 (45.83%)
Symptom	
Headache	20 (83.33%)
Nausea and vomiting	17 (70.83%)
Loss of vision	18 (75.00%)
Unilateral visual decline	11 (45.83%)
Bilateral visual decreased	6 (25.00%)
Complete loss of unilateral vision	0
Complete loss of bilateral vision	1 (4.17%)
Visual field defects	8 (33.33%)
Bitemporal hemianopia	6 (25.00%)
Unilateral hemianopia	2 (8.33%)
Cranial nerve palsy	7 (29.17%)
Altered mental status	1 (4.17%)
Decreased libido	2 (8.33%)
Amenorrhea/oligomenorrhea	2 (8.33%)
Galactorrhea	1 (4.17%)

Hormone levels (free thyroxine, thyroid-stimulating hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, estrogen, prolactin [PRL], cortisol, and human growth hormone [GH]) were measured postoperatively to assess pituitary function regardless of preoperative hypopituitarism. We excluded stroke events on the first postoperative day from the head CT scan of all patients. Routine follow-up was conducted at 3 and 6 months and 1 and 3 years after surgery to assess resolution of clinical symptoms such as headache and decreased vision; hormone examination and MRI of the sellar region were also carried out. The first postoperative magnetic resonance imaging was obtained 3 months after surgery to determine the extent of tumor resection. Gross total removal (GTR) was defined as no visible remnant tumor on the first postoperative MRI. A residual tumor of less than 5% was considered near-total resection (NTR), subtotal resection (STR) was considered to be performed with tumor remaining between 5% and 25%, and tumor remnants greater than 25% were considered partial resection. Tumor recurrence during follow-up was defined as an increase in the size of the tumor growth or residual tumor that was not previously detected on MRI.

### Surgical Technique

Under general anesthesia, the patient was supine with the head tilted back 15°. The nasal cavity was first decongested with cotton pledgets soaked in 0.01% epinephrine saline. A rigid 30° endoscope with an outer diameter of 4 mm (Karl Storz SE & Co. KG) was introduced into the dilated right nostril. The sphenoid sinus opening was located 1.5 cm above the root of the middle turbinate. An arc-shaped pedicled nasoseptal flap was created on the nasal septum 1 to 2 cm above the inner margin of the sphenoid sinus opening. The anterior wall of the sinus was penetrated with a high-speed microdrill to enlarge the opening and expose the upper end of the pyriform bone, which was then drilled to enlarge the bone window. The septum of the sphenoid sinus was drilled and the mucosa was removed, providing a complete view of the sellar floor. After identifying the optic canal and bulge of the internal carotid artery canal, a bone window with a diameter of about 1.5 cm was created at the bottom of the saddle using a high-speed microdrill and neurodissector. A small sickle-shaped blade was used to open up the dura, and an aspirator and curler were used to remove the tumor, with care taken to avoid the pituitary gland and arachnoid by adjusting the angle of the endoscope as needed. After PA, the pituitary is squeezed to the top or side as the pressure in the sellar increases. Carefully read the MRI to identify the compressed and thinned pituitary and avoid injury (Figure 1A and B). At the same time, the operation is gentle to reduce the pull on the pituitary gland and the pituitary stalk. To remove the tumor, the tumor in the slope direction should be removed first, and then the tumor on both sides should be removed, so as to avoid the premature decline of the sellar diaphragm. The tumor cavity was filled with Gelfoam and Surgicel (Ethicon, Somerville) and the skull base was repaired



**Figure 1.** (A and B) Recognition of pituitary gland under endoscope. Endoscopic field of view shows the compressed and thinned pituitary gland (white arrow) just below the diaphragm sella after tumor resection.

with artificial dura and medical glue (Kangpaite). The pedicled nasoseptal flap was applied to the outermost layer.

For patients with intraoperative cerebrospinal fluid (CSF) leakage, the sandwich technique was used to repair the bottom of the sellar region in 3 layers. The tumor cavity was first filled with autologous fat, which was covered with an artificial dura mater, with medical glue applied for reinforcement. For the second layer, pieces of Gelfoam wrapped in Surgicel were used as a base and the outer layer was coated with muscle paste and covered with a layer of artificial dura mater, with the medical adhesive used for bonding. In order to tightly seal the saddle bottom, the fascia lata was used as the third layer outside the muscle and was bonded with medical adhesive. Finally, the pedicled nasoseptal flap was rotated over the graft. At the end of the surgery, the nasal cavity was stuffed with an expanding sponge.

## Results

### Patient Demographics

A total of 24 cases (13 males and 11 females) with a mean age of  $46.46 \pm 14.95$  years (range: 18-66 years) were included in the analysis (Table 1), accounting for 9.45% (24 of 254) of EETA surgery in the same period. The mean follow-up time was  $25.16 \pm 10.25$  months (range: 7-48 months).

### Symptoms and Signs

Most patients presented with sudden-onset headache ( $n=20$ , 83.33%) and nausea and vomiting ( $n=17$ , 70.83%) (Table 1). The most frequent symptoms of PA were loss of vision ( $n=18$ , 75.00%), in which 8 patients (33.33%) had visual field defect, followed by and ophthalmoplegia ( $n=7$ , 29.17%), which were mainly attributable to third and sixth cranial nerve palsy. Patients also had decreased libido ( $n=2$ , 8.33%), amenorrhea ( $n=2$ , 8.33%), and lactation ( $n=1$ , 4.17%). Only 1 patient

(4.17%) experienced a sudden onset of consciousness that did not improve with administration of supplemental hormones at admission. According to the PA Grading System (Table 2), 19 patients (79.17%) were Grade 5, 3 (12.50%) were Grade 4, and 2 (8.33%) were Grade 3.

### Imaging Findings

All patients had previously undetected pituitary macroadenomas; the average maximum tumor diameter was  $2.55 \pm 0.65$  mm (range: 14-39 mm) on MRI (Table 3). Ten adenomas (41.67%) showed cavernous sinus infiltration (Table 4).

### Endocrine Findings

Endocrine examination at the time of admission revealed normal endocrine function in 7 of 24 cases and hypopituitarism in 10 of 24 cases. There were 7 cases of hormonally active adenomas, with high blood concentrations of PRL in 3 cases; 1 case each of GH, adrenocorticotrophic hormone (ACTH), and gonadotropin; and 1 case of mixed ACTH and PRL (Table 3).

### Surgical Results and Follow-Up

The first postoperative MRI confirmed total resection in 21 cases (87.50%) and STR in 3 cases (12.50%). In the latter,

**Table 2.** Pituitary Apoplexy Grading System.

Grade	Clinical presentation
1	Asymptomatic
2	Endocrinologic deficit only
3	Headache (acute onset or acute-to-chronic)
4	Ophthalmoplegia due to oculomotor cranial nerve palsies Ocular paresis (cavernous sinus cranial nerves)
5	Visual disturbances or decreased consciousness Visual acuity or field deficit (or low Glasgow Coma Scale precluding testing)

**Table 3.** Types of Secretory Activity in 24 Patients with Pituitary Apoplexy.

Tumor type	Number of adenomas			Total	Percentage
	11-20 mm	21-30 mm	>30 mm		
PRL	1	1	1	3	12.50
ACTH	0	1	0	1	4.17
GH	1	0	0	1	4.17
GnH	0	1	0	1	4.17
ACTH + PRL	0	1	0	1	4.17
Nonsecreting	1	4	2	7	29.17
Hypopituitarism	1	5	4	10	41.67
Total	4	13	7	24	100.00

Abbreviations: ACTH, adrenocorticotrophic hormone; GH, growth hormone; GnH, gonadotropin; PRL, prolactin.

complete excision was not possible because of the firm nature of the tumor (2 cases) and apparent infiltration of the tumor into the cavernous sinus (1 case); 2 of the patients relapsed during follow-up, and 1 underwent reoperation while the other received gamma knife treatment.

Headache was resolved in all patients; 4 of the 7 patients with cranial nerve palsy fully recovered within 3 months after surgery and the other 3 showed improvement. The patient with disturbance of consciousness returned to normal consciousness after surgery. All patients were postoperatively evaluated for visual acuity and endocrine function. The vision was improved in 17 of 18 patients (94.44%) with reduced vision, but the patient with complete loss of vision preoperatively did not improve after the surgery. No patient experienced a new or worsening decline in visual acuity. At the last follow-up, ophthalmoplegia had resolved in all of the patients and vision was completely normal in 14 (77.78%), improved in 3 (16.67%), and unchanged in 1 patient (5.56%). Serum pituitary hormone levels declined to normal or near normal in 6 of 7 patients (85.71%) with functional adenomas, and bromocriptine was orally administered to 1 patient with a prolactinoma to achieve disease control. Postoperative hormone levels were improved to varying degrees in the 10 patients with hypopituitarism, and in 5 the hormone levels returned to normal without medication during follow-up.

### Complications

There were no complications such as intracranial infection, carotid injury, or death in our case series. CSF leakage occurred in 2 patients during surgery, and sandwich skull base reconstruction was performed without lumbar cistern drainage. The patients ultimately recovered and were discharged. Four

**Table 4.** Knosp Grade of 24 Patients with Pituitary Apoplexy.

Grade	Number (%)
0	14
1	3
2	5
3	2

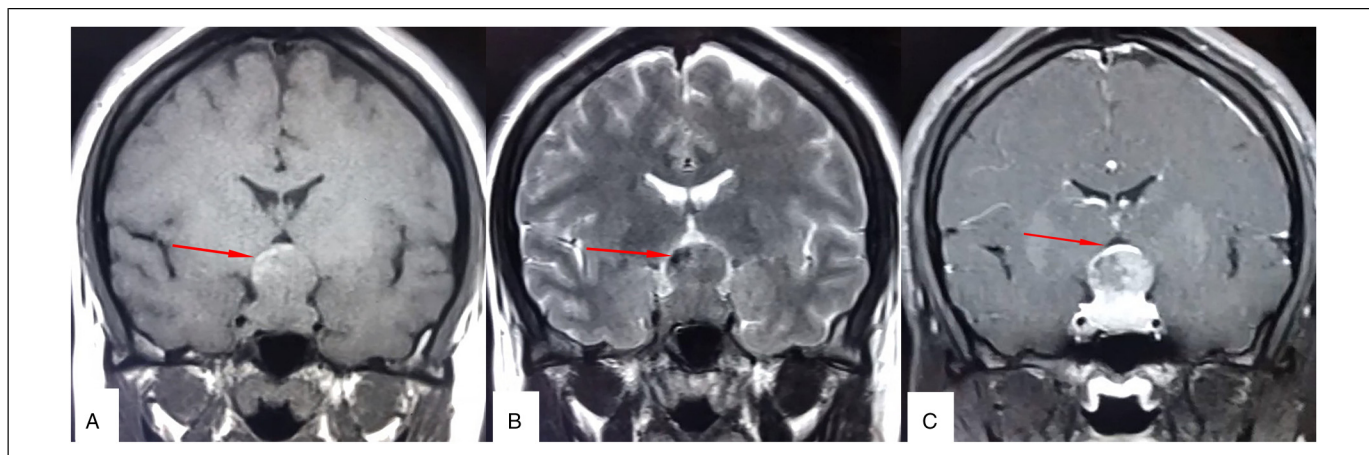
patients developed diabetes insipidus after surgery; urination was gradually controlled after pituitrin supplementation. Only 1 patient required oral administration of desmopressin acetate to control urination after discharge from the hospital, and urine volume was normal 3 months after surgery without the need for drugs.

The case of a 24-week pregnant woman in our series warrants special mention. The patient was admitted for a blurred vision that had persisted for 1 week and headache with nausea and vomiting lasting 1 day. Head MRI revealed a gourd-like lesion measuring about 2.8 cm in length in the sellar region. Both T1- and T2-weighted images were dominated by isointense signals, and a small high-intensity mixed signal was observed at the edge of the lesion in the T1 image (Figure 2A). In the T2 image, it was a mixed slightly hypointense signal (Figure 2B). Additionally, the tumor showed uneven enhancement (Figure 2C). Endocrine examination revealed normal levels of anterior pituitary hormones. After surgical treatment, the patient's symptoms of headache and vision defects were significantly improved, but she developed transient urinary collapse and thyroid axis dysfunction. At 38 weeks of gestation, she gave birth to a healthy baby boy. Subsequent follow-up revealed complete resection of the tumor and restoration of normal thyroxine axis function.

### Discussion

PA is a rare clinical syndrome that occurs mostly in men and peaks in the fifth decade of life.<sup>1-3</sup> Our series showed a male predominance (54.17%).<sup>12,14,17</sup> As observed in our study, PA is common in cases of nonfunctioning pituitary macroadenomas and may occur as the first manifestation of a pituitary tumor,<sup>18</sup> which lack hormonal effects and are not diagnosed until the tumor becomes large enough to cause symptoms due to mass effects or the occurrence of PA.

The pathophysiologic basis of PA remains unclear; it is thought to be related to tumor growth, insufficient blood supply, abnormal (immature) vascularization, and overexpression of vascular endothelial growth factor.<sup>19-21</sup> Although multiple risk factors have been identified including hypertension, cardiac surgery, laparoscopic surgery, pituitary stimulation



**Figure 2.** (A-C) Magnetic resonance imaging (MRI) of the patient with pituitary apoplexy. (A, B) The MRI scan revealed a lesion that was isointense in both T1- and T2-weighted images, and a small slightly hypointense mixed signal was observed at the edge of the lesion in the T2 image (red arrow). In the T1 image, it was a mixed high-intensity signal (red arrow). (C) Additionally, the tumor showed uneven enhancement with compressed and thinned pituitary gland above (red arrow).

tests, thrombocytopenia, anticoagulants, craniocerebral trauma, and pregnancy,<sup>6-11,19,22-24</sup> in most cases PA occurs naturally,<sup>25</sup> typically presenting as a sudden-onset thunderclap-like headache accompanied by reduced vision, ophthalmoplegia, and hypopituitarism. These symptoms are due to increased pressure in the sellar region caused by a sudden increase in the volume of the pituitary adenoma, which peripherally compresses structures such as the optic nerve, third ventricle, cavernous sinus, and pituitary gland.

In our series, 83.33% of patients had a headache, 70.83% had nausea and vomiting, 75.00% had diminished vision, and 29.17% had ophthalmoplegia. Similar incidences of these clinical symptoms were reported in recent case series of PA.<sup>26</sup>

Once PA is suspected, a cranial MRI should be performed unless the patient cannot be examined. The sensitivity of CT is 21% to 46%, while that of MRI—which can provide information regarding a stroke—is as high as 90%.<sup>27</sup> In our study, iso- or slightly hypointense signals in T1-weighted images and hypointense signals in T2-weighted images were observed in the acute phase (<7 days); in the subacute phase (7-21 days), the signal in both T1 and T2 images gradually increased as a result of the degradation of red blood cells. Classic PA is associated with sphenoid sinus mucosal thickening, which was observed in 27 of 39 patients (69%) with neurologic deficits compared to 1 patient (14%) without deficits.<sup>28</sup> At a later stage, stratification of the solid and liquid states can also be observed in the saddle area due to deposition of blood products. Thus, PA has a variable presentation on MRI.

Initial emergency management for PA included mandatory steroid therapy and management of the internal environment. Unstable internal environment or pituitary dysfunction may lead to increased perioperative risks for patients. Patients' vital signs, mental status, urine volume, blood sodium levels, and body fluid balance were routinely monitored while neurological, endocrine, ophthalmic, and other assessments were performed after admission. However, whether conservative or

surgical treatment was the best treatment has always been the focus of controversy, especially for those patients with moderate symptoms.<sup>29</sup> Bujawansa et al<sup>30</sup> suggest that conservative treatment is appropriate for selected patients with mild and non-progressive neuro-ophthalmic defects, but this requires long-term follow-up. Khodayar's studies have shown that there is no significant difference in vision and endocrinology between surgery and conservative treatment.<sup>31</sup>

We believe that the risk–benefit ratio of a conservative treatment to surgery must be carefully evaluated, taking into account not only the visual outcome and pituitary function but also subsequent tumor growth. Appropriate conservative management is as beneficial as surgical management. However, because all reported case series were analyzed retrospectively, there is a selection bias for more severe cases that require surgical treatment. As such, we only evaluated therapeutic efficacy based on patients who received surgical treatment for PA. According to the UK's PA management guidelines of 2010, early surgery (<8 days) is recommended for patients with obvious neuro-ophthalmic defects and disturbance of consciousness whose ophthalmic symptoms fail to improve or worsen during conservative treatment. However, in one study, patients who had surgery within 72 h of symptom onset showed no significant differences in vision, ophthalmoplegia, and endocrine findings compared to those who had surgery after 72 h<sup>14</sup>; and similar findings for headache or vision outcomes were reported in patients treated by surgery within 7 days of symptom onset versus over 7 days later.<sup>32</sup> It is our experience that surgery should be performed regardless of timing in patients with significant visual impairment, preferably at a dedicated pituitary treatment center. Because of the inherent limitations of diagnostic systems in many areas, early surgery may not be possible in some patients. As in our case, 14 of the 18 patients with vision loss underwent surgery 7 days after onset, but they all had varying degrees of postoperative improvement in vision.

Simple ophthalmoplegia can be treated conservatively. However, we usually resort to endoscopic surgery to promote recovery from ophthalmoplegia because it can affect the quality of life of the patient, especially in those who are younger. Ophthalmoplegia was alleviated in all of our patients, with the recovery of normal vision in 77.78% and vision improvement in 16.67%. At the same time, the endocrine results were encouraging: 50% of patients did not require long-term endocrine replacement therapy at the last follow-up and there was no new hypopituitarism, which was slightly higher than outcomes reported at other centers.<sup>32</sup> This may be due to the correct recognition and protection of the adenohypophysis and pituitary stalk during sellar region surgery. Pituitary dysfunction can occur after stroke as a result of compression or destruction of the pituitary gland, disruption of the blood supply to the gland, or injury to the pituitary stalk.<sup>33</sup> The relationship between pituitary protection and postoperative pituitary function in the sellar region surgery has been a hot topic in recent years.<sup>34,35</sup>

CSF leakage is one of the most common complications of transnasal endoscopic surgery and depends on the characteristics of the tumor, surgical technique, and experience of the operator. Postoperative CSF leakage is mainly due to a failure to recognize or repair the problem during surgery. As PA is more common in macroadenomas with mostly suprasellar extension, there is an increased risk of CSF leakage. We used a pediculated septal flap that was rotated to cover the sellar floor irrespective of intraoperative CSF leakage. Although the application of a nasal septum flap increases the risk of olfactory dysfunction in patients, this outcome is preferable to postoperative CSF leakage or catastrophic intracranial infection. When intraoperative CSF leakage is detected, the skull base can be reconstructed using the sandwich technique. For high-flow CSF leaks, remedial lumbar drainage is necessary. Two patients with intraoperative CSF leakage in our series received remedial treatment and were discharged. There was no occurrence of endoscopy-related complications such as intracranial infection, vascular injury, or death, although 4 patients experienced transient urinary collapse after the surgery.

There were some limitations to our study. The main shortcoming was that it was a nonrandom retrospective analysis of a small number of cases at a single institution, which precluded a multivariate analysis. Additionally, some patients had a short follow-up time, which may have influenced the endocrine findings. Finally, the surgeries were performed by an experienced surgeon at a tertiary pituitary center, and the results may not be applicable to all institutions.

## Conclusion

PA is a rare clinical syndrome that is common in pituitary macroadenomas. Patients with visual defects, ophthalmoplegia, and confusion usually require surgical treatment. Our case series demonstrates that EETA is safe and effective for the treatment of PA. Headache and ocular symptoms are resolved in most patients, but postoperative endocrine defects often persist; this

warrants further study so that better clinical outcomes can be achieved.

## Authors' Contributions

ZS, XC, and ZJ designed the study. ZS, YL, and DS analyzed the data. ZS, XC, YL, and YL wrote the manuscript. ZJ revised the manuscript and supervised the study. All authors approved the final version of the manuscript for publication.

## Authors' Note

Zhixiang Sun, Xintao Cai, these authors contributed equally to this work.

## Data Availability

The data generated in this study can be requested from the corresponding author.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.



## Ethics Approval and Informed Consent

This study was approved by the Research Ethics Committee of Bengbu Medical College (no. 2020025). The need for informed consent was waived by the Research Ethics Committee because the study was retrospective. The confidentiality of patient data was protected in accordance with the tenets of the Declaration of Helsinki.

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